Functional MRI entropy measurements of age-related brain changes

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INTRODUCTION

The health and robustness of a system can be measured in terms of the complexity of its output (Goldberger, 2002). Systems with complex output patterns are thought to be better able to respond to perturbation and damage, minimising functional loss.

As we age there is a decline in cognitive abilities such as processing speed, memory, executive function and reasoning.. The basis for this decline is not well understood although it is reasonable to assume that at its origin is the accumulation of age and disease specific pathology. How the brain mediates the effects of this pathological burden to maintain function is unclear. The complexity of longitudinal physiological measurements such as electroencephalogram (EEG) (Gaal et al, 2010) has been shown to vary with age and disease which may represent a decrease in the capacity to cope with age and disease.

Nonlinear dynamic analysis techniques such as Approximate Entropy (ApEn) can be applied to characterize the changes in brain complexity. A high ApEn indicates unpredictability and high complexity, whereas low ApEn indicates predictability and low complexity (Pincus, 1991).

The aim of this study is to examine the complexity changes in the brain by calculating the approximate entropy (ApEn) of 'resting state' fMRI time series on a voxel by voxel basis, creating maps of entropy across the brain. We hypothesize that ApEn will be less in middle age (>40 years) when compared to a younger sample.

METHODS

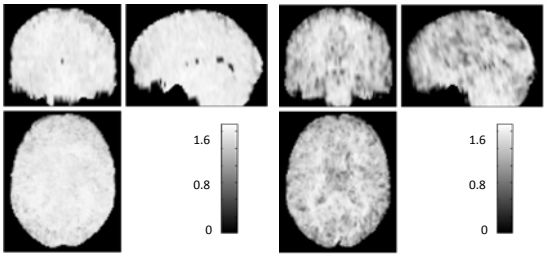
Twenty healthy volunteers ranging from age 25 to 60 years (8 male) were recruited for the present study. Participants were recruited into the study by locally advertising on notice boards and the intranet. They were divided into two groups: the younger group (n=11) of volunteers with age ranging from 25 to 40 and the older group (n=9) of volunteers with ages between 42 to 60 years.

The study was approved by the local Research Ethics Committee. A detailed written and verbal explanation of the purpose and design of the study was provided to all the volunteers and written informed consent obtained prior to the commencement of the study.

FMRI data were acquired using a T2* weighted gradient-echo echo-planar imaging sequence (EPI) in the axial plane with TR/TE of 2000/30 ms, matrix 128 X 128, field of view of 24 cm^2, thickness of 3.5 mm, 28 slices per volume (600 time points/volumes were acquired after discarding the first 4 volumes).

Whole brain ApEn maps for each individual were generated on a voxel by voxel basis on a MATLAB platform.

Statistical analysis was performed on a global basis with SPSS and on a regional basis with SPM8 and the Wakeforest PickAtlas (v 2.5.2).



(a) (b)

Figure 1: 3D whole brain ApEn maps. (a) 25 years old participant from the younger group with whole brain mean ApEn of 1.3891 (b) 60 years old participant from the older group with whole brain mean ApEn of 1.1453.

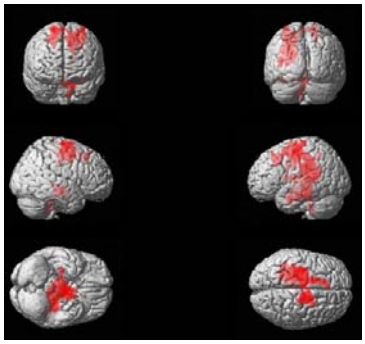


Figure 2: Regions in the brain showing difference in ApEn between the older and younger groups. Older group has lower signal ApEn when compared to the younger group in the regions in red.

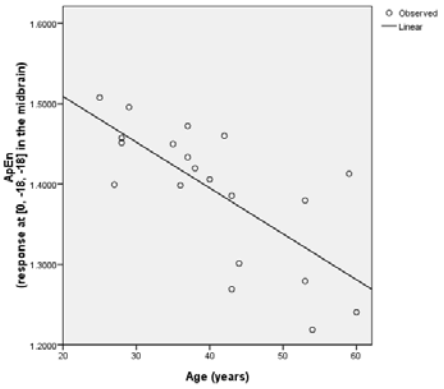


Figure 3: Association between ApEn and age (ApEn is negatively correlated with age

Table 1: Individual ROIs analysed using the Wakeforest PickAtlas tool

Region of interest	Talairach coordinate (XYZ)	Hemisphere	Brain label	Cluster p value (corrected)	Voxel t value	Extent
Whole brain white matter	-24 -36 38	Left	Sub-Gyral	0.000	5.46	3985
	-28 -32 22	Left	Extra-Nuclear		4.89	
	-24 -16 54	Left	Precentral Gyrus		4.78	
Frontal Lobe	-24 -36 38	Left	Sub-Gyral	0.001	5.46	2453
	-24 -16 54	Left	Precentral Gyrus	0.029	4.78	1012
	-28 -34 26	Left	Sub-Gyral		4.50	
	14 -8 68	Right	Superior Frontal Gyrus		4.13	
	14 -4 60	Right	Medial Frontal Gyrus		4.10	
	22 -16 54	Right	Sub-Gyral		3.86	
Sub-Lobar	-28 -32 22	Left	Extra-Nuclear	0.001	4.89	1900
	-2 -20 0	Left	Third Ventricle		4.65	
	-10 -32 0	Left	Pulvinar		4.17	
Midbrain	-4 -10 -16	Left	Midbrain	0.002	4.74	1391
	-2 -22 -2	Left	Midbrain		4.54	
	4 -20 -14	Right	Midbrain		4.22	
Medulla	-6 -38 -44	Left	Medulla	0.040	3.20	22

RESULTS

Figure 1 depicts the 3D ApEn map of the whole brain for 25 and 60 years old participants of the younger and older groups respectively.

The mean ApEn values for the younger and older groups were 1.31(±0.09) and 1.24(±0.10) respectively. No significant global ApEn differences were found between the younger and older groups ($p<0.05$).

When the data was tested regionally with family wise error (FWE) corrected cluster level significance of $p<0.05$, the result of the two-sample t-test ($p=0.005$) is shown in Figure 2. The discriminated regions (in red) in Figure 2 show significant differences in ApEn between the younger and older groups. Here, the older group has lower ApEn when compared to the younger group.

Figure 3 shows that ApEn correlates negatively with age (at a corrected cluster level significance of $p<0.05$) i.e. ApEn reduces with increase in age.

A region of interest (ROI) analysis on the differences in ApEn between the younger and older groups shows significant ($p<0.05$) decline in the ApEn of the older group as shown in the Wakeforest PickAtlas ROI analysis listed in Table 1.

No significant correlation was found between ApEn and gender ($p<0.05$).

CONCLUSIONS

Our results represent a novel observation with regard to how we age. We observed that there are regions in the brain where there is a decline in ApEn values with age i.e. brain complexity decreases with age.

Some regions identified such as white matter, frontal lobe and midbrain have previously been found to be associated with brain ageing. Bartzokis et al. (2001) found that there is a decrease in grey matter volume between adulthood and old age, whereas white matter volume was found to increase from age 19-40, and decline after this age. In addition Craik and Salthouse, (2000) found that the frontal lobe is affected by age-related processes resulting in a decline in memory functions. Staff et al. (2006) found that sub-lobar white matter structures are associated with generalised cognitive ageing. Our analysis also found a reduction in ApEn due to age in the sub-lobar and medulla.

Our findings may represent a response to the accumulated burden and indicate that the networks underpinning function are compromised and less able to respond to damage, eventually resulting in functional loss. These findings in terms of location are consistent with observed structural changes with ageing and may represent the capacity of these locations to overcome these age related structural changes and maintain function.

ACKNOWLEDGEMENTS

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